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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/547,999	09/07/2006	Daniel Portnoy	B01-050 (BERK-017CIP)	6366
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UC Berkeley - OTL Bozicevic, Field & Francis LLP 1900 University Avenue, Suite 200 East Palo Alto, CA 94303			EXAMINER DUFFY, PATRICIA ANN	
			ART UNIT	PAPER NUMBER
			1645	
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			12/01/2009 PAPER	

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/547,999

Applicant(s)

PORTNOY ET AL.

Examiner

Patricia A. Duffy

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 8-13-09.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14, 15, 25, 26 and 28-32 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14, 15, 25, 26 and 28-32 is/are rejected.
- 7) ☒ Claim(s) 33-35 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB06)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

RESPONSE TO AMENDMENT

The previous office action mailed 11-25-09 improperly indicated that it was non-final. The non-final action mailed 11-25-09 is hereby withdrawn and a final rejection is newly mailed. The time period for response is started from the mail date of this final office action.

The amendment filed 8-13-09 has been entered into the record. Claims 1-13, 16-24 and 27 have been cancelled. Claims 14, 15, 25, 26 and 28-35 are pending and under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Maintained

Claim 14, 15, 25, 26 and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Frankel et al (US Patent No. 6,099,848, issued August 8, 2000) in view of Frazao et al (WO 99/07861, published 18 February 1999) and Loessner et al (Molecular Microbiology, 35(2):324-340, 2000) is maintained for all reasons made of record.

Applicant's arguments have been carefully considered but are not persuasive. Applicants argue and impermissible obvious to try standard and Applicants submit that, in view of the art discussed further below, one of ordinary skill in the art would have had no such beliefs. Accordingly, and contrary to the Examiner's assertions, the ordinary skilled artisan would not have predicted with any reasonable expectation of success that a listeriophage attP site identified in silico by Loessner et al. could provide for an integration vector capable of integrase mediated site-specific Listeria genome integration, which in turn would provide for cells that are transformed with an integration vector capable of integrase mediated site-specific Listeria genome integration as recited by the pending claims. Applicants present multiple references to indicate that the references as

combined do not teach how to modify the attachment sites to provide for site-specific integration because sequences outside of the attachment site may be required and as such the skilled artisan would not believe that such could be substituted. This is not persuasive, the skill in this art is very high and the determination of such mere routine. The use of phage attachment sites in integration vectors is so standard in this art that chapters have been written on the subject (Smith et al eds *Methods in Microbiology*, Volume 29, *Genetic Methods for Divers Prokaryotes*, Academic Press Inc. 1999, pages 117-118.) For example, Smith et al teach that "Plasmids that integrate site-specifically into the bacterial chromosome to give a stable single copy insertion are relatively easy to construct and are used widely." Smith et al go on to indicate that "The ease with which these vectors can be constructed has meant that characterization of the integrase has become a primary aim in the analysis of any new phage or integrating plasmid." (page 117) Smith et al also teach the routine means of identifying the components for integration and means for identification of such using search algorithms from PROSITE and PFAM (page 118, last paragraph). As such, the identification of attachments sites capable of integration is routine in this highly developed art. Such is also exemplified by art, as the art is replete with the use of two vector and single vector site specific integration vectors using phage attachment sites. See for example Yang et al (*Journal of Bacteriology*, 184(7):1859-1864, 2002), Rossignol et al (*FEMS Microbiology Letters*, 213:45-49, 2002); Moreau et al, (*Microbiology* 145:539-548, 1999), Luong et al, (*Journal of Microbiological Methods* 70:186-189, 2007 citing Lee et al *Gene* 103:101-105, 1991), McShan et al (*Methods in Cell Science* 20:51-57, 1998) and Lillehaug et al (*Gene* 188:129-136, 1997) all of which teach integration vectors containing bacteriophage integrases and attachment sites for site-specific gene insertion. Therefore, it is the position of the office that the art in this area is highly developed and that the combination provides for a reasonable expectation of success where multiple bacteriophage attachment sites and integrases from numerous other bacteria have been successfully used to make and use site-specific

integration vectors and are in wide use in the art. Therefore, in view of the routine nature of construction of site specific vectors comprising bacteriophage attachment sites and integrases from numerous other bacteria, one skilled in this art would have a reasonable expectation of success. Applicants argue that the attachment sites and integrases of the combination are untested. Merely, because the sequences are untested does not indicate that they are ineffective for the intended purpose as combined and the identification and use of such were characterized by the art as relatively easy to construct. Applicants argue that the metes and bounds of the attachment site differ between bacteria and use of one cannot predict use of any other. This is not persuasive because the characterization of the attachment site for use in the integration vector is routine in the art. Applicants argue that the ordinary skilled artisan would have believed that it unreasonable to expect that a postulated attachment site from any phage would be function outside the context of the phage genome. This is not persuasive in view of the wide use of bacteriophage attachment sites in site-specific integration vectors. 35 USC 103 does not require absolute prediction of success but a reasonable expectation thereof. In view of the plethora of successes in the art, the skilled artisan would reasonably have been able to use the information on attachment sites in Listeriophages to construct a *Listeria* site-specific integration vector for use in the method as claimed. Applicants references indicate that it is clear that the skilled artisan would have been aware in certain instances that sequences surrounding the attachment site were required for integration. The position of the office is that it is routine to determine the attachment site for competent integration and that the art as combined directs one skilled in the art to construction of site-specific integration vectors for *Listeria*, that making integration competent site-specific vectors in general for the bacterial art was routine and widespread in the art and that the identified sequences as combined function for their intended purpose. Applicants arguments indicating a lack of reasonable expectation of success and impermissible obvious to try are therefore not persuasive.

For these and all the other reasons of record the rejection maintained.

Status of Claims

Claims 14, 15, 25, 26 and 28-34 stand rejected. Claims 33, 34 and 35 are objected to as depending from the rejected independent claim.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 7:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisors, Robert Mondesi can be reached at 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/
Primary Examiner